Preoperative Dexamethasone Improves Surgical Outcome After Laparoscopic Cholecystectomy

A Randomized Double-Blind Placebo-Controlled Trial

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Objective: To determine the effects of preoperative dexamethasone on surgical outcome after laparoscopic cholecystectomy (LC).

Summary Background Data: Pain and fatigue are dominating symptoms after LC and may prolong convalescence.

Methods: In a double-blind, placebo-controlled study, 88 patients were randomized to intravenous dexamethasone (8 mg) or placebo 90 minutes before LC. Patients received a similar standardized anesthetic, surgical, and multimodal analgesic treatment. All patients were recommended 2 days postoperative duration of convalescence. The primary endpoints were fatigue and pain. Preoperatively and at several times during the first 24 postoperative hours, we measured C-reactive protein (CRP) and pulmonary function, pain scores, nausea, and number of vomiting episodes were registered. Analgesic and antiemetic requirements were recorded. Also, on a daily basis, patients reported scores of fatigue and pain before and during the first postoperative week and the dates for resumption of work and recreational activities.

Results: Eight patients were excluded from the study, leaving 40 patients in each study group for analysis. There were no apparent side effects of the study drug. Dexamethasone significantly reduced postoperative levels of CRP ($P = 0.01$), fatigue ($P = 0.01$), overall pain, and incisional pain during the first 24 postoperative hours ($P < 0.05$) and total requirements of opioids ($P < 0.05$). In addition, cumulated overall and visceral pain scores during the first postoperative week were significantly reduced ($P < 0.05$). Dexamethasone also reduced nausea and vomiting on the day of operation ($P < 0.05$). Resumption of recreational activities was significantly faster in the dexamethasone group versus placebo group (median 1 day versus 2 days) ($P < 0.05$).

Conclusion: Preoperative dexamethasone (8 mg) reduced pain, fatigue, nausea and vomiting, and duration of convalescence in patients undergoing noncomplicated LC, when compared with placebo, and is recommended for routine use.

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Laparoscopic cholecystectomy (LC) is one of the most common elective surgical procedures in the western world.[1] Duration of convalescence after noncomplicated LC may depend on several factors of which pain, fatigue, and sociocultural factors are the most important.[2,3] Pain and fatigue are most intense on the day of operation and the following day.[2,4] Nausea and vomiting occur mainly on the day of operation and only rarely contribute to prolonged convalescence.[2]

Glucocorticoids are well known for their analgesic, antiinflammatory, immune-modulating, and antiemetic effects, although the mechanisms by which glucocorticoids exert their action are far from clarified.[5] Several randomized, clinical trials in many different major and minor surgical procedures have been conducted to examine the effects of a perioperative single-dose glucocorticoid administration on surgical outcome.[6] The overall results on postoperative outcome have either been positive in favor of the glucocorticoid group or without differences between study groups, with postoperative nausea and vomiting and pain as outcome parameters most significantly improved.[6–8] Data from LC have shown questionable effects in pain, nausea, and vomiting,[9–11] but with higher satisfaction and shorter stay in the day-care unit.[9]

We therefore undertook the present study to investigate whether preoperative dexamethasone could improve surgical outcome in patients undergoing uncomplicated LC. Our primary endpoints were overall pain and fatigue the first day after operation and during the first postoperative week. We also investigated the effects of dexamethasone on nausea and vomiting and duration of convalescence.

METHODS

From February 1999 to November 2000, 88 patients were randomized. The criteria of exclusion were ASA physical class III or IV, age > 75 years, pregnancy, and patients having papillotomy by endoscopic retrograde cholangiopancreatography (ERCP) within 1 month before and during the first month after operation. Patients were not included if they had chronic pain diseases other than gallstone disease; any

signs of endocrine, renal, hepatic, or immunologic diseases; or if they received opioids or tranquilizers (treatment of > 1 week before LC); in case of foreign language or mental disorder; or if they had a history of alcohol or drug abuse. Patients were excluded if the operation was converted from LC to open procedure or if an additional fifth trocar was needed to complete the operation. Finally, since development of surgical complications might influence the chosen outcome parameters, we decided before study start to exclude these patients from the study and results were analyzed by the protocol.

Patients were followed from the day before operation and daily during the first postoperative week. Day of operation was defined as day 0 and the first day after operation as day 1, etc. A 30-day follow-up for morbidity was performed in all cases. The present study included several contacts between patients and study observers during the first postoperative 24-hour period. Accordingly, for practical reasons patients were routinely admitted the first night after the operation (Table 1).

Surgery, Anesthesia, Analgesia, and Antiemetics

Pneumoperitoneum was created at the supraumbilical port site with a closed Verres needle technique. LC was performed by the standard French technique (surgeon standing between the patient's legs) using 2 10-mm and 2 5-mm trocars with standard nondisposable laparoscopic equipment. The gallbladder was retracted via the supraumbilical 10-mm trocar port. Whenever necessary, in both surgical groups, a lateral fascial incision was made (0.5–1 cm) to ease retraction of the gallbladder. The need for fascial incision was not systematically registered. Only the fascia at the supraumbilical port site was closed using a resorbable suture. The skin at all port sites was closed using nonresorbable sutures. Gentamicin (160 mg) was given at the beginning of surgery.[4] During laparoscopy, intraabdominal pressure was maintained at 12 mmHg. CO_2 was carefully evacuated at the end of surgery by manual compression of the abdomen with open trocars. Operations were conducted or supervised by experienced laparoscopic surgeons (equally distributed between the 2 surgical groups). All patients received a similar general anesthesia (Table 1) using fentanyl, propofol, cisatracurium, and alfentanil as described elsewhere.[12] In the postoperative anesthesia care unit (PACU), vital signs (blood pressure, pulse, respiration, pulse oximetry, and adequate answering) were monitored every 15 minutes by a consultant. Patients were discharged from PACU when vital signs were normalized. We used a prophylactic multimodal analgesic technique for treatment of postoperative pain.[12] Thus, patients received incisional local anesthetics in all port sites using a total 140 mg of bupivacaine (0.5% bupivacaine, 10 mL in the supraumbilical incision and 6 mL in each of the other 3 incisions with a technique described previously).[12] Intravenous ketorolac (30 mg) was given approximately 20 minutes before end of surgery; in the recovery room, patients received 2 g of paracetamol as suppositories. Three hours postoperatively, oral treatment with ibuprofen (600 mg eight-hourly for 4 days) was commenced (patients were given prepacked envelopes with ibuprofen for self-administration to cover the first 4 days). Patients were carefully instructed to take the prophylactic analgesic medicine even though they had no pain. Additional morphine was administered if needed either intravenously (5–10 mg in the PACU) or orally (20–30 mg in the ward). Intravenous ondansetron (4 mg) was administered for antiemetic treatment on demand. Opioid rescue medication was not given at discharge from hospital, but it was prescribed by general practitioners where needed. Supplementary postoperative medication on day of operation (Table 1) was defined as medication in addition to the multimodal postoperative prophylactic standard analgesic treatment described above.

Patients were discharged from hospital when fully mobilized and vital signs were normalized.

Pain and Fatigue

Pain was registered preoperatively, several times during the first 24 postoperative hours, and daily during the first postoperative week. Incisional pain was defined as superficial pain, wound pain, or pain located in the abdominal wall. Visceral pain was pain inside the abdomen, which may be deep, dull, and more difficult to localize, and/or may resemble biliary colic. Shoulder pain was defined as pain in the shoulder. Overall pain was defined as a composite of incisional, visceral, and shoulder pain.[4,12] These parameters were measured on a visual analogue scale (VAS) with end points labeled "no pain" and "worst possible pain" and on a verbal rating scale (VRS) (no pain = 0, light pain = 1, moderate pain = 2, severe pain = 3). The same 2 study investigators (TB or BK) recorded pain at rest (supine) and during mobilization (supine to sitting)[12,13] preoperatively and 1, 2, 3, 6, and 24 hours after operation (ie, investigator-recorded instant pain scores). In addition, patients themselves registered overall pain (VAS) and incisional pain, visceral pain, and shoulder pain (VRS) (self-reported registrations). Self-reported registrations were done the day before operation (at 8 pm), at the day of operation (6 hours postoperatively; at 6 hours postoperatively both the investigator-recorded instant pain scores and patients self-registered pain scores were recorded), and daily until postoperative day 7 at 8 pm. At the same intervals, patients also rated fatigue on a 10-point ordinal scale (fit = 1, fatigued = 10).[14] Patients were instructed that self-reported registrations should cover pain and fatigue within the time period since last measurements.[2,4,13]

Postoperative Nausea and Vomiting (PONV)

Patients evaluated nausea and vomiting over 2 postoperative intervals 0 through 6 hours and 6 through 24 hours after operation.[15] Nausea was rated on a VRS (no nausea = 0, mild nausea = 1, moderate nausea = 2, severe nausea = 3), and the number of vomiting episodes were registered (no episodes were scored as none = 0; 1 episode as mild = 1; 2 or 3 episodes as moderate = 2; more than 3 episodes as severe = 3).

Pulmonary Function

Pulmonary function was evaluated using a spirometer (Micro Plus Spirometer; Micro Medical Limited, Rochester, England) with the patient in the sitting position by measuring peak flow rate (l min^{-1}), forced vital capacity (l) (FVC), and forced expired volume in first second (l) (FEV_1). Assessments were performed preoperatively and 1, 2, 3, 6, and 24 hours after operation. At each session, the best of 3 attempts was recorded. At the same time, oxygen saturation, (SpO_2

TABLE 1. Patient Characteristics and Perioperative Data

	Dexamethasone (n = 40)	Placebo (n = 40)
Patient characteristics		
Sex ratio (M:F, no.)†	13:27	7:33
Age (years)‡	46 (27–72)	39 (22–69)
Body mass index (kg/m^2)‡	26 (20–41)	25 (28–39)
ASA physical class (I:II, no.)†	33:7	34:6
Previous motion sickness (no.)†	23	19
Previous PONV (no.)†	13	11
History of smoking (no.)†	17	16
Operative data and general anesthesia		
Duration of surgery (min.)‡	78 (30–205)	68 (35–190)
Intraoperative cholangiography (no.)§	3	4
Fentanyl (mg)‡	0.2 (0.1–0.3)	0.2 (0.2–0.3)
Propofol (mg)‡	1506 (845–3830)	1341 (165–3677)
Cisatracurium (mg)‡	10 (6–25)	10 (5–20)
Alfentanil (mg)‡	3.0 (1.0–8.0)	2.5 (0.0–6.0)
Saline infusion IV (mL)‡	1000 (500–1900)	900 (400–1700)
Postoperative data		
stay in PACU (min)‡	75 (35–169)	70 (15–240)
stay in hospital (nights)‡	1 (1–2)	1 (1–2)
Supplementary postoperative medication on day of operation#		
Opioids		
Number of patients requiring§	8	16
Total dose (mg)‡	110	255*
Median dose (mg)‡	0 (0–30)	0 (0–35)*
Ondansetron		
Number of patients requiring§	8	15
Total dose (mg)‡	40	80
Median dose (mg)‡	0 (0–4)	0 (0–8)

Patients' characteristics, operative data and general anesthesia, postoperative data, and supplementary postoperative medication in 80 patients randomized to preoperative dexamethasone or placebo. PONV = postoperative nausea and vomiting. # Supplementary postoperative medication was medication in *addition* to the postoperative prophylactic standard analgesic treatment described above on the day of operation (by the study investigators) and daily during the first postoperative week (by the patients) in a study log. Values are given as median (range) and number of patients (no.).

* $P < 0.05$. Surgical groups were statistically compared using (□) Chi-square, (□) Mann-Whitney, and (§) Fisher exact tests.

(%)) by spot check, was measured with a portable pulse oximeter using a finger probe (Nellcor N-20; Nellcor Puritan Bennett Inc., Pleasanton, CA, USA).

Convalescence

Duration of convalescence was defined as the number of postoperative days (including the day of operation) away from work and main recreational activities.[2] All patients were recommended 2 days postoperative convalescence. Workload and/or recreational activities were preoperatively stratified as sedentary, light, moderate, or severe. The date patients resumed a fulltime workday and their main recreational activity was noted in a structured questionnaire as reported previously.[2]

Blood Samples

Venous blood was drawn from the cubital vein on the preoperative morning (before the test solution was given) 6 and 24 hours after start of the operation. C-reactive protein (CRP) was measured in serum by the nephelometric method (Dade Behring; N *High Sensitivity* CRP, Vitros Chemistry) with a detection limit of 0.9 mg/L (manufacturer's data).

Body Temperature

Before the drug/placebo was given and at 6 and 24 hours after the skin incision, rectal temperature was measured using an electronic thermometer (PIC Indolor; Artsana S.p.A. Garandate, Italy) with a sensitivity $\pm$ 0.1°C (manufacturer's data).

Randomization

Patients were randomized by the sealed envelope method (on the basis of a block-randomized computer-generated list), and the randomization code was kept separate and not known to any of the investigators until the study was finished. Patients were randomized to receive dexamethasone (8 mg; Decadron; Merck Sharp & Dome, Glostrup, Denmark) intravenously 90 minutes before skin incision or saline (placebo). The drug/placebo solution was drawn into a syringe by a nurse not participating in the study and was delivered to the investigator (TB) who was outside the medicine room and unaware of the content. The saline and dexamethasone solutions appeared transparent and completely identical at the time syringes were given to the investigator. Thus, the patient, the anesthesiologist, the surgeon, and the study observer were all blinded with respect to the study group. The study drug was administered to the patient within 5 minutes after drawn into the syringes.

Statistics, Sample Size, and Ethics

For statistical analyses, we used Mann-Whitney, Friedman, Fisher exact test, χ^2, Spearman rank correlation coefficients, and Log Rank tests when appropriate. Postoperative 24-hour results were specifically analyzed for intergroup differences. In addition, repeated postoperative scores at different time points of fatigue and overall pain were added together for intergroup comparison (added total pain scores and added total fatigue scores). The association between total dose of postoperative supplementary opioids (during hospital stay) and the added total VAS scores of overall pain (during mobilization covering the first 24-hour period) were examined using the Spearman rank correlation coefficients. Nausea and vomiting scores were evaluated separately for the 0 through 6-hour period and the 6 through 24-hour period. From each period, the highest severity score and highest incidence of nausea and vomiting were used as a measure of nausea and/or vomiting for the entire 24-hour period. $P < 0.05$ was considered statistically significant, and data are given as median (range) if not stated otherwise.

Sample size calculation was based on added total VAS scores of overall pain during first week from 53 consecutive patients and added total fatigue scores from 108 consecutive patients undergoing uncomplicated LC receiving a similar anesthetic and analgesic treatment as placebo patients in the present study.[2] With a power to detect a minimal relevant difference (MIREDIF) between surgical groups of 50% and a type 1 and 2 error of 0.05 and 0.20, respectively, 39 patients in each group would be adequate. We included 2×44 patients in the study.

The local ethics committee and the Danish Health Authorities approved the study, and all patients gave their written informed consent to participate in the study.

RESULTS

Eighty patients were available for analysis (Table 1), and 8 patients (four in each treatment group) were excluded from the study (see below: Side Effects and Complications).

Fatigue

Fatigue increased significantly in both groups ($P < 0.01$, Friedman tests) (Fig. 1a). In the dexamethasone group, fatigue scores were significantly lower 24 hours after operation ($P < 0.01$, Mann-Whitney U test) and throughout the postoperative week compared with the placebo group ($P = 0.01$, Friedman test). The added total postoperative fatigue scores were median 28 (8–54) and 32 (8–67) in the dexamethasone and placebo group, respectively ($P = 0.01$, Mann-Whitney U test).

Pain

Pain scores during the first 24 hours at rest and mobilization are shown in Figure 2a-c (for clarity, only VAS results are shown; statistical results from VRS scores were comparable with the VAS results). In both surgical groups, shoulder pain scores were median zero at all assessments. Patients in the dexamethasone group suffered significantly less overall pain, incisional pain, and visceral pain 24 hours after operation ($P < 0.05$, Mann-Whitney tests). The added total scores (covering the entire 24-hour period) of overall

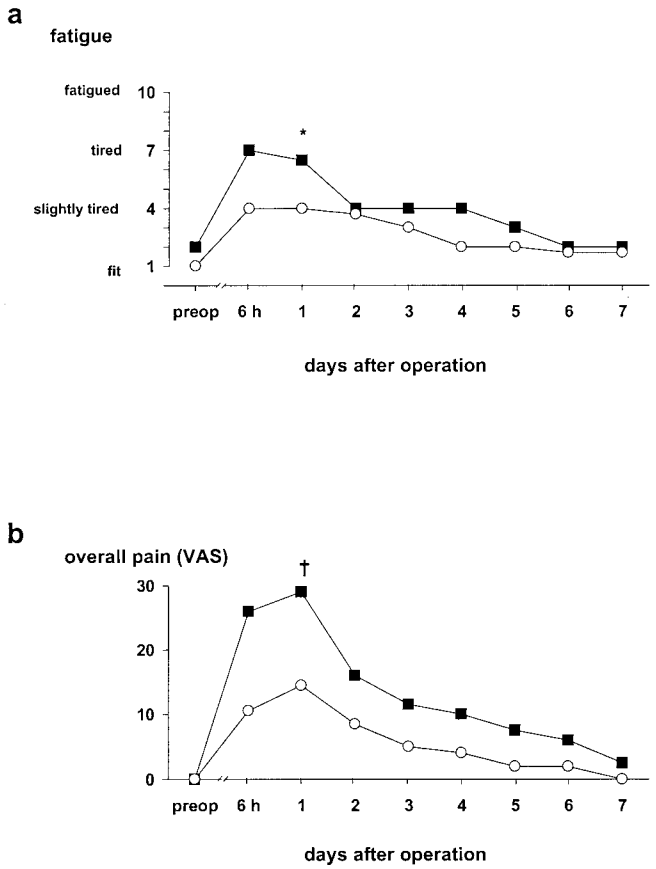

FIGURE 1. Changes in (a) fatigue scores and (b) overall pain scores in patients receiving (○) dexamethasone (n = 40) or (■) placebo (n = 40) before laparoscopic cholecystectomy. Patients who received dexamethasone were significantly less fatigued on postoperative day 1 (*$P < 0.05$) and throughout the study period ($P = 0.01$) and suffered significantly less overall pain on postoperative day 1 (†$P < 0.01$). Cumulated fatigue and pain scores were significantly lower in the dexamethasone group (see text for details). Values are median; VAS, visual analogue scale.

pain and incisional pain during mobilization were significantly lower in the dexamethasone group ($P < 0.05$, Mann-Whitney tests), whereas there were no significant differences in the other added instant pain scores (ns). Intergroup differences for changes in pain scores during the entire 24-hour test period were not significant (ns, Friedman tests).

In the dexamethasone group, self-reported VAS scores for overall pain were significantly lower at day 1 after operation compared with the placebo group (Fig. 1b) ($P < 0.05$, Mann-Whitney *U* test). The added total VAS scores of overall pain (covering the first postoperative week) were median 53 (0–265) (dexamethasone group) and 157 (6–434) (placebo group), respectively ($P < 0.01$, Mann-Whitney *U* test). In both treatment groups, self-reported scores of overall pain increased during the first postoperative week ($P < 0.01$, Friedman tests), but differences between groups did not change significantly during the test period ($P = 0.10$, Friedman test). The added total VRS scores (covering the first postoperative week) of incisional, visceral, and shoulder pain in the dexamethasone versus placebo group were 5 (0–9) versus 6 (0–14) ($P = 0.21$, Mann-Whitney *U* test), 3 (0–11) versus 5 (0–15) ($P < 0.05$), and 1 (0–11) versus 2 (0–11) ($P = 0.26$). On postoperative day 1, the number of patients in dexamethasone versus placebo group reporting incisional, visceral, and shoulder pain (light/moderate/severe) were 30 versus 34 patients ($P = 0.26$, χ^2 test), 23 versus 32 patients ($P < 0.05$), and 16 versus 20 patients ($P = 0.37$).

Analgesic Requirements

Eight patients in the dexamethasone group and 16 patients in the placebo group, respectively, required 1 or more supplementary doses of morphine during their hospital stay ($P = 0.09$, Fisher exact test) with a significantly lower total dose of morphine in the dexamethasone group ($P < 0.05$, Mann-Whitney *U* test) (Table 1). Spearman correlation coefficients for the association between the total dose of postoperative supplementary opioids during hospital stay and overall pain (first 24-hour period) were 0.55 ($P < 0.01$) and 0.59 ($P < 0.01$) for the dexamethasone and placebo groups, respectively. After discharge from hospital, 0 patients in the dexamethasone group and 5 patients in the placebo group required supplementary opioids (in total, opioids were taken 10 times by 5 different patients) ($P = 0.06$, Fisher exact test). After discharge from hospital, 24 patients in the dexamethasone group and 21 patients in the placebo group required supplementary paracetamol or NSAIDs or both on 1 or more days ($P = 0.65$, χ^2 test).

Nausea and Vomiting

During the first 6 postoperative hours, the incidence and severity of nausea was significantly lower ($P < 0.05$, χ^2 test and Mann-Whitney *U* test) in the dexamethasone group, and vomiting was significantly reduced during the entire 0 through 24-hour period compared with placebo ($P < 0.05$, χ^2 test and Mann-Whitney *U* test) (Table 2). Eight patients in the dexamethasone group versus 15 in the placebo group received intravenous ondansetron for antiemetic treatment once or more during their hospital stay ($P = 0.14$, Fisher exact test) (Table 1).

Pulmonary Function

Peak flow, FVC, and FEV_1 decreased in both groups postoperatively ($P < 0.01$, Friedman tests) with no significant intergroup differences (*P*-values not statistically significant,

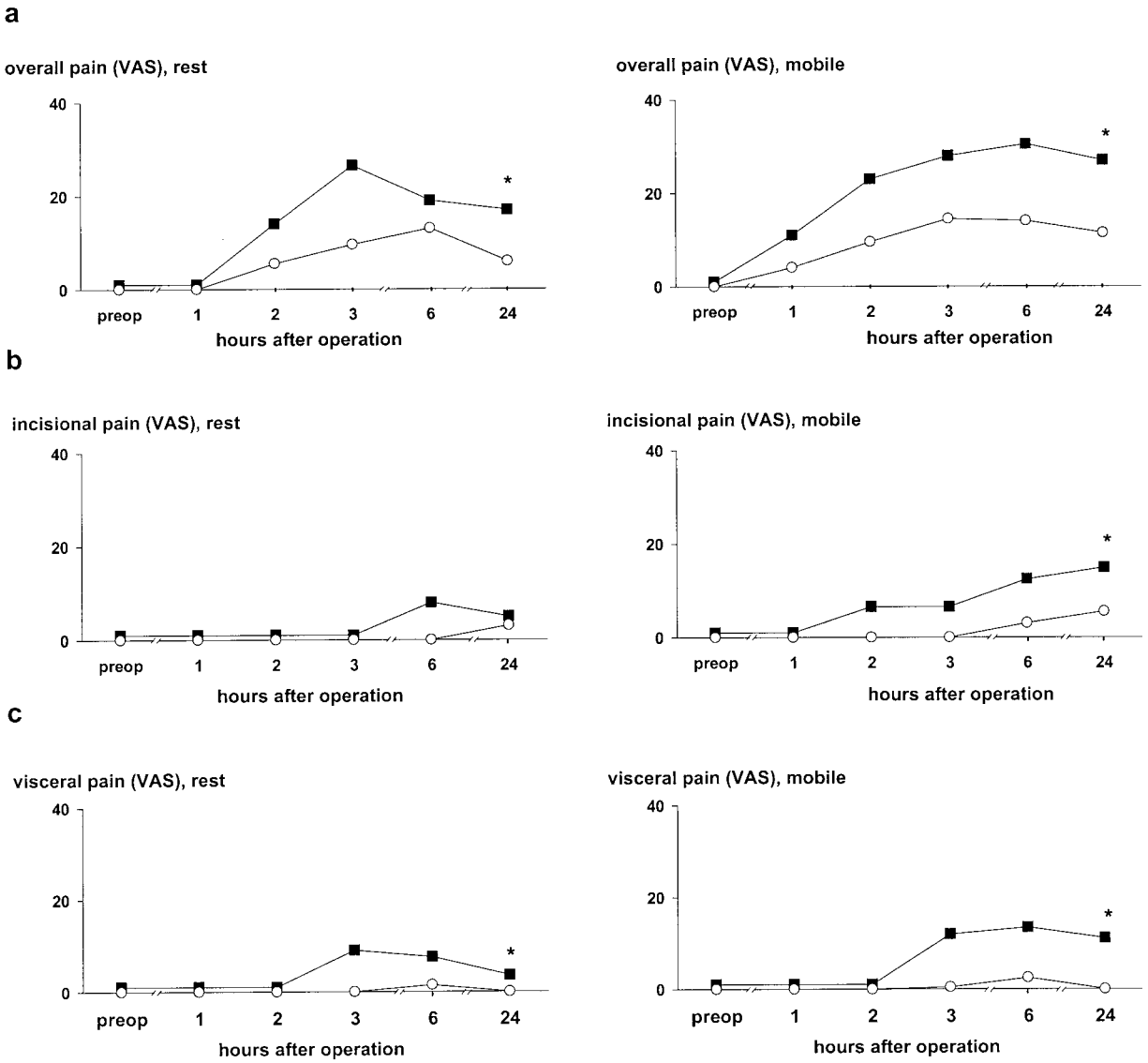

FIGURE 2. Changes in scores of (a) overall pain, (b) incisional pain, and (c) visceral pain in patients receiving (○) dexamethasone (n = 40) or (■) placebo (n = 40) during the first 24 hours after laparoscopic cholecystectomy. Total added pain scores for overall pain and incisional pain during mobilization were significantly lower in the dexamethasone group (see text for details). Shoulder pain scores are not shown since median scores throughout the study period were zero in both study groups with no significant intergroup difference (see text). Values are median; VAS = visual analogue scale. *$P < 0.05$.

Friedman tests) (Fig. 3a-c). SpO_2 in the dexamethasone group increased slightly, but significantly, compared with the placebo group ($P < 0.01$, Friedman test) (Fig. 3d).

Convalescence

In the dexamethasone group, recreational activities (n = 40) were resumed after median 1 day (0–7) versus 2 days (0–13) in the placebo group (n = 40) ($P = 0.03$, Log Rank test). In the dexamethasone group, work (n = 29) was resumed after median 5 days (1–19) versus 5 days (1–25) in the placebo group (n = 29) ($P = 0.52$, Log Rank test). Duration of stay at the PACU and hospital was not significantly different between surgical groups (Table 1).

C-Reactive Protein

Serum CRP increased significantly in both treatment groups during the study period ($P < 0.01$, Friedman tests), but the increase was significantly higher in the placebo group ($P < 0.01$, Friedman tests) (Fig. 4a).

TABLE 2. Postoperative Nausea and Vomiting

	Dexamethasone (n = 40)	Placebo (n = 40)
0–6 hours after surgery		
PONV (no.)‡	11	20
nausea (no.)‡	10	19*
no/mild/moderate/severe§	30/9/1/0	21/16/2/1*
vomiting (no.)‡	1	10†
no/mild/moderate/severe§	39/1/0/0	30/7/2/1†
6–24 hours after surgery		
PONV (no.)‡	5	7
nausea (no.)‡	5	6
no/mild/moderate/severe§	35/5/0/0	34/5/1/0
vomiting (no.)‖	1	3
no/mild/moderate/severe§	39/1/0/0	37/3/0/0
entire 24-hour period		
PONV (no.)‡	13	21
nausea (no.)‡	12	19
no/mild/moderate/severe§	28/11/1/0	21/16/2/1
vomiting (no.)‡	2	10*
no/mild/moderate/severe§	38/2/0/0	30/7/2/1*

Results of self-reported postoperative nausea and/or vomiting (PONV) over two postoperative intervals 0 through 6 hours and 6 through 24 hours and entire 24-hour period in 80 patients randomized to preoperative dexamethasone or placebo. Values are numbers of patients (no.).

*$P < 0.05$; †$P < 0.01$. Surgical groups were statistically compared using (□) Chi-square, (§) Mann-Whitney, and (‖) Fisher exact tests.

Body Temperature

Body temperature rose significantly in both groups during the study period ($P < 0.01$, Friedman tests) without significant intergroup difference ($P = 0.5$, Friedman test) (Fig. 4b).

Side Effects and Complications at 30-day Follow-Up

No apparent signs of side effects of the study drug were observed. Four patients in each study group were excluded from the study. In the dexamethasone group, 2 patients had cholecystectomy performed using an additional trocar (5-port cholecystectomy), since a laparoscopic paddle retractor was used to lift the liver to avoid conversion to open procedure. In 1 patient, preoperative cholangiography revealed a retained stone in the common bile duct, and endoscopic retrograde cholangiography (ERCP) with stone extraction was performed the next day. One patient developed an infection in the umbilical incision (skin opened 5 days after operation). In the placebo group, the operation was converted to open procedure in 2 patients (due to dense abdominal adhesions), 1 patient withdrew from the study postoperatively, and 1 patient developed an infection in the umbilical incision (skin opened 6 days after operation for drainage). Thus, 2 patients (one from each study group) developed postoperative wound infections.

DISCUSSION

This study basically demonstrated that intravenously administered dexamethasone (8 mg) 90 minutes before LC significantly reduced postoperative fatigue, pain, nausea, and vomiting and that patients resumed recreational activities significantly faster when compared with placebo.

A possible association between glucocorticoids and impaired wound healing and postoperative infections or other complications is a major concern. In our study, we found no apparent side effects or complications to the dexamethasone treatment, since only 1 patient in each surgical group developed a postoperative wound infection. Similarly, no other randomized, clinical trials in any type of surgery using high doses of methylprednisolone or any doses of dexamethasone have reported a significant increase in infectious or all-over complications.[6] A recent meta-analysis[16] concluded that perioperative administration of high-dose methylprednisolone (30–35 mg/kg), a dose approximately 50 times the dose used in our study, was not associated with significant side effects. The meta-analysis included trials of major surgical procedures, combined with studies in trauma and spinal cord injury. Also, from a recent meta-analysis on postoperative nausea and vomiting, a single varying dose of dexamethasone did not increase infectious complications or other complications.[7] Therefore, we believe that there is evidence to support that single-dose preoperative treatment with dexamethasone (8 mg) is safe in otherwise healthy patients in minor procedures such as LC.

Glucocorticoids are important modifiers of the postoperative physiologic inflammatory, humoral, and immunologic responses by regulation of the trauma-induced humoral mediators.[5] In the present study, significant increases in CRP levels and body temperature were observed in both treatment groups, but CRP levels (and fatigue scores) increased significantly less in the dexamethasone group compared with placebo. Thus, our findings suggest that intravenous dexamethasone administered 90 minutes preoperatively reduced the postoperative inflammatory response after LC in accordance with observations from other procedures.[6] Several studies have reported only transient postoperative fatigue after LC, returning to preoperative levels within the first postoperative week.[2,17–19] It has been suggested that early postoperative fatigue after LC may be related to sleep disturbances and the inflammatory response during the first 2–3 postoperative days.[3,20] Our findings of reduced levels of CRP and fatigue scores in the dexamethasone group support that early fatigue may be associated with the short-lasting inflammatory response after LC. These results are supported by the findings of increased fatigue and reduced sleep after interleu-

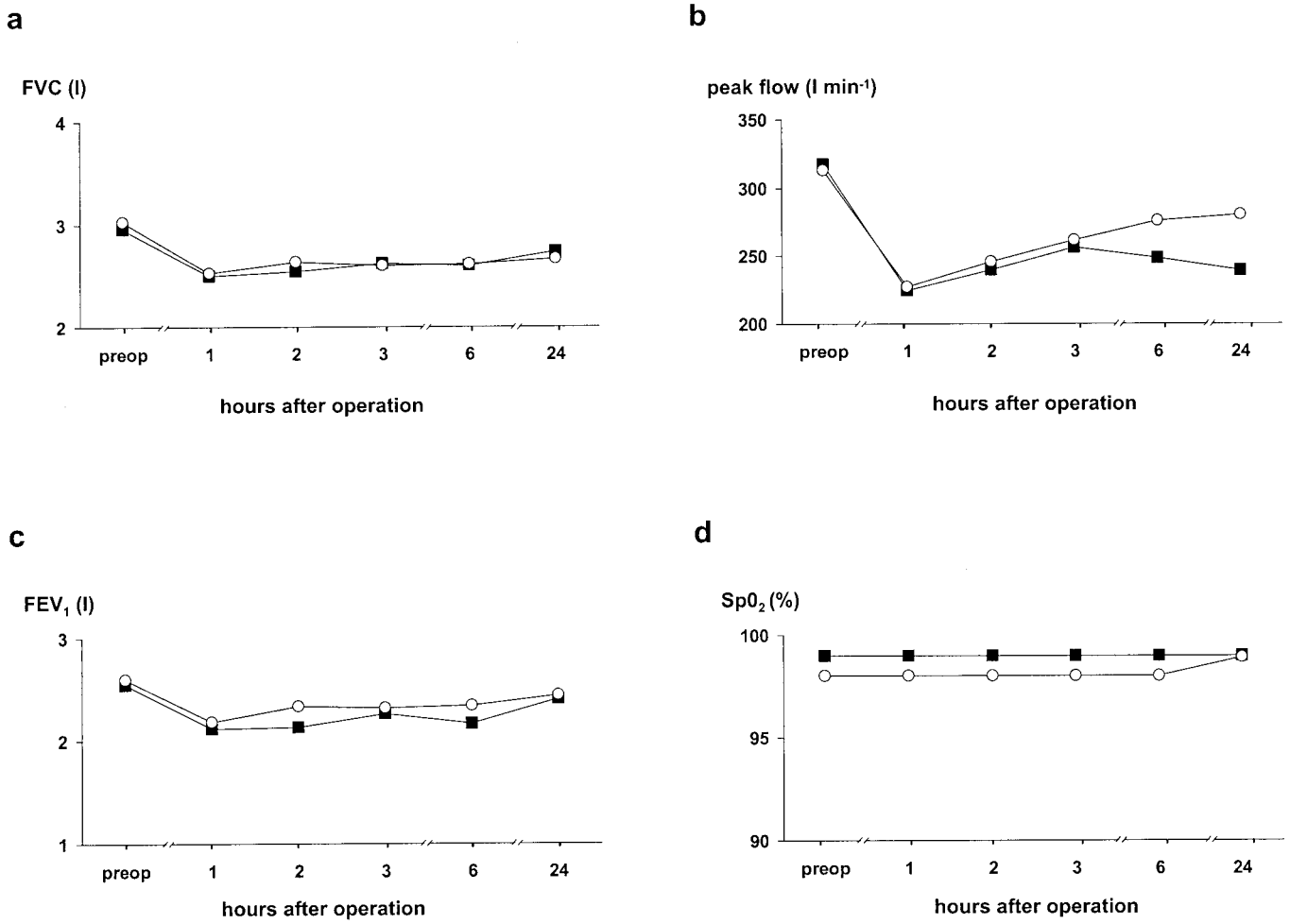

FIGURE 3. Changes in (a) forced vital capacity (FVC), (b) peak flow, (c) forced expiratory volume in 1 second, and (d) oxygen saturation (SpO_2) during the first 24 hours after laparoscopic cholecystectomy in patients randomized to preoperative (○) dexamethasone (n = 40) or (■) placebo (n = 40). There were no significant intergroup differences except for SpO_2 intergroup changes during the study period ($P < 0.01$).

kin-6 infusion in human volunteers.[20] Only 2 other trials including patients undergoing major abdominal surgery have studied the effect of preoperative glucocorticoids (high-dose methylprednisolone) on fatigue.[21,22] There were no significant differences in fatigue scores, but postoperative mobilization was significantly improved in the glucocorticoid groups.[21,22]

The analgesic effects of glucocorticoids are provided through inhibition of the phospholipase enzyme and accordingly blockage of both the cyclooxygenase and the lipoxygenase pathway in the inflammatory chain reaction,[5] as well as suppressing tissue levels of bradykinin[23] and release of neuropeptides from nerve endings[24], both of which may enhance nociception in inflamed tissue and the surgical wound. In the present study, dexamethasone reduced overall pain, as well as incisional and visceral pain, but not shoulder pain. However, since the intensity and incidence of shoulder pain were minimal, the contribution to patients' sensation of overall pain was probably limited. Our results are corresponding to the analgesic effects of dexamethasone (8 mg) in patients undergoing gynecologic operations[25] and dental extractions.[26] In a recent review[6] regarding the effects of perioperative single-dose glucocorticoid administration, randomized trials from several minor and major surgical procedures were analyzed.[6] The authors concluded that glucocorticoid administration in major abdominal surgery probably has no or limited analgesic effects, but may have analgesic effects in minor surgical procedures, and finally that glucocorticoids definitely have analgesic effects in dental surgery.[6]

The mechanism by which glucocorticoids alleviate nausea and vomiting is not fully understood, but the effects

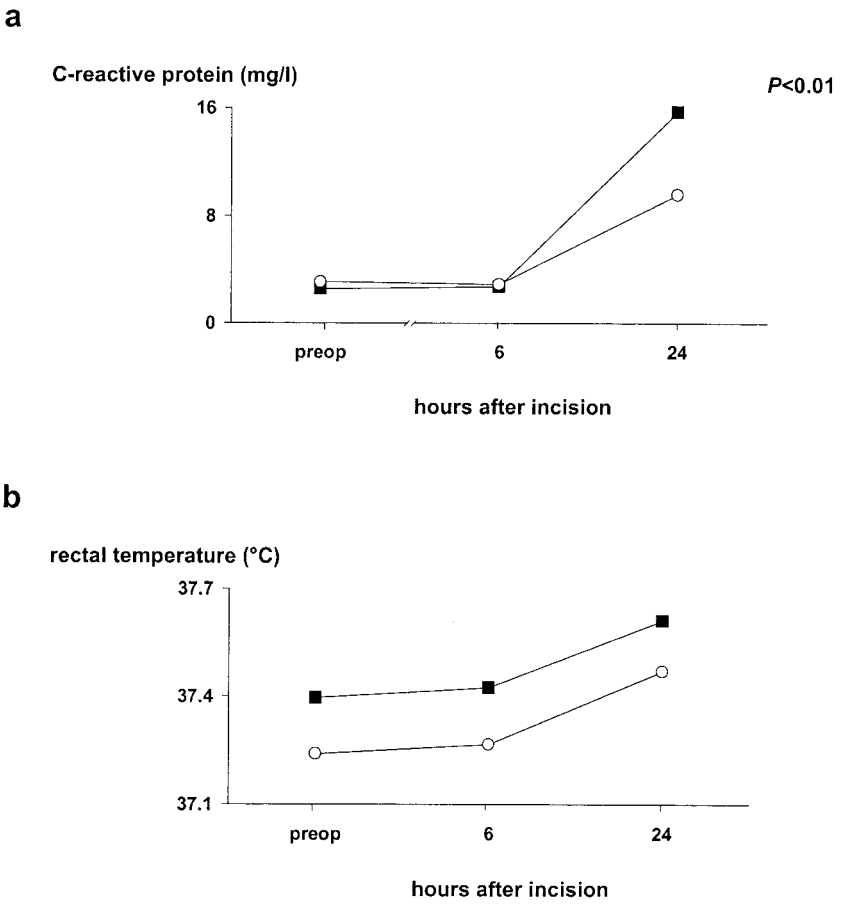

FIGURE 4. Changes in (a) serum C-reactive protein (CRP) levels and (b) body temperature in patients receiving (○) dexamethasone (n = 40) or (■) placebo (n = 40) before laparoscopic cholecystectomy. The increase in CRP was significantly higher in the dexamethasone group ($P < 0.01$). There were no intergroup differences in body temperature during the test period ($P = 0.5$). Values are median.

are probably centrally mediated via inhibition of prostaglandin synthesis or inhibition of the release of endogenous opioids.[7] In a recent meta-analysis of 17 randomized controlled trials, a single dose of dexamethasone in combination with 5-HT_3 receptor antagonists significantly reduced postoperative nausea and vomiting when compared with placebo, but the optimal dose of this combination still needs to be identified.[7] Furthermore, the role of concomitant use of 5-HT_3 receptor antagonists remains to be clarified.[8–11]

In the present study, intravenous dexamethasone was administered 90 minutes before skin incision. Glucocorticoids bind to the intracellular glucocorticoid receptor, and effects are predominantly mediated through an altered protein-synthesis via gene transcription.[27] Therefore, onset of biologic action is generally 1–2 hours, depending on the route of administration.[5] Unfortunately, most studies have used administration of glucocorticoids immediately before induction of anesthesia,[6] including the other trials in patients undergoing LC.[9–11] Since activation of the early mediators of the metabolic response to surgery occurs immediately after the surgical incision, administration of glucocorticoids 1–2 hours preoperatively may be of importance to achieve full postoperative benefit of the treatment.[28]

In conclusion, dexamethasone improved surgical outcome after LC in terms of significantly less pain, fatigue, nausea, and vomiting, and patients resumed their recreational activity significantly faster compared with the placebo group. Since the regimen used is safe and without apparent side effects, we suggest that preoperative dexamethasone should be used as routine in otherwise healthy patients undergoing elective LC.

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REFERENCES

1. Johnson A. Laparoscopic surgery. *Lancet*. 1997;349:631–635.
2. Bisgaard T, Klarskov B, Rosenberg J, et al. Factors determining convalescence after uncomplicated laparoscopic cholecystectomy. *Arch Surg*. 2001;136:917–921.
3. Bisgaard T, Kehlet H, Rosenberg J. Pain and convalescence after laparoscopic cholecystectomy. *Eur J Surg*. 2001;167:84–96.
4. Bisgaard T, Klarskov B, Rosenberg J, et al. Characteristics and prediction of early pain after laparoscopic cholecystectomy. *Pain*. 2001;90: 261–269.
5. Sapolsky RM, Romero LM, Munck AU. How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. *Endocr Rev*. 2000;21:55–89.
6. Holte K, Kehlet H. Perioperative single dose glucocorticoid administration—Pathophysiological effects and clinical implications. *J Am Coll Surg*. 2000;195:186–712.
7. Henzi I, Walder B, Tramer MR. Dexamethasone for the prevention of postoperative nausea and vomiting: a quantitative systematic review. *Anesth Analg*. 2000;90:186–194.
8. Fujii Y, Saitoh Y, Tanaka H, et al. Granisetron/dexamethasone combination for the prevention of postoperative nausea and vomiting after laparoscopic cholecystectomy. *Eur J Anaesthesiol*. 2000;17:64–68.
9. Coloma M, White PF, Markowitz SC, et al. Dexamethasone in combination with dolasetron for prophylaxis in the ambulatory setting. Effect on outcome after laparoscopic cholecystectomy. *Anesthesiology*. 2002; 96:1346–1350.
10. Wang JJ, Ho ST, Liu YH, et al. Dexamethasone reduces nausea and vomiting after laparoscopic cholecystectomy. *Br J Anaesth*. 1999;83:772–775.
11. Wang JJ, Ho ST, Uen YH, et al. Small-dose dexamethasone reduces nausea and vomiting after laparoscopic cholecystectomy: a comparison of tropisetron with saline. *Anesth Analg*. 2002;95:229–232.
12. Bisgaard T, Klarskov B, Kristiansen VB, et al. Multi-regional local anesthetic infiltration during laparoscopic cholecystectomy in patients receiving prophylactic multi-modal analgesia: a randomized, double-blinded, placebo-controlled study. *Anesth Analg*. 1999;89:1017–1024.
13. Bisgaard T, Klarskov B, Trap R, et al. Microlaparoscopic vs conventional laparoscopic cholecystectomy. *Surg Endosc*. 2002;16:458–464.
14. Christensen T, Stage JG, Galbo H, et al. Fatigue and cardiac and endocrine metabolic response to exercise after abdominal surgery. *Surgery*. 1989;105:46–50.
15. Greif R, Laciny S, Rapf B, et al. Supplemental oxygen reduces the incidence of postoperative nausea and vomiting. *Anesthesiology*. 1999; 91:1246–1252.
16. Sauerland S, Nagelschmidt M, Mallmann P, et al. Risks and benefits of preoperative high dose methylprednisolone in surgical patients: a systematic review. *Drug Safety*. 2000;23:449–461.
17. Jakeways MS, Mitchell V, Hashim IA, et al. Metabolic and inflammatory responses after open or laparoscopic cholecystectomy. *Br J Surg*. 1994;81:127–131.
18. Kristiansson M, Saraste L, Soop M, et al. Diminished interleukin-6 and C-reactive protein responses to laparoscopic versus open cholecystectomy. *Acta Anaesthesiol Scand*. 1999;43:146–152.
19. Troidl H, Spangenberger W, Langen R, et al. Laparoscopic cholecystectomy: technical performance, safety and patient's benefit. *Endoscopy*. 1992;24:252–261.
20. Spath-Schwalbe E, Hansen K, Schmidt F, et al. Acute effects of recombinant human interleukin-6 on endocrine and central nervous sleep functions in healthy men. *J Clin Endocrinol Metab*. 1998;83:1573–1579.
21. Nagelschmidt M, Fu ZX, Saad S, et al. Preoperative high dose methylprednisolone improves patients outcome after abdominal surgery. *Eur J Surg*. 1999;165:971–978.
22. Schulze S, Andersen J, Overgaard H, et al. Effect of prednisolone on the systemic response and wound healing after colonic surgery. *Arch Surg*. 1997;132:129–135.
23. Hargreaves KM, Costello A. Glucocorticoids suppress levels of immunoreactive bradykinin in inflamed tissue as evaluated by microdialysis probes. *Clin Pharmacol Ther*. 1990;48:168–178.
24. Hong D, Byers MR, Oswald RJ. Dexamethasone treatment reduces sensory neuropeptides and nerve sprouting reactions in injured teeth. *Pain*. 1993;55:171–181.
25. McKenzie R, Tantisira B, Karambelkar DJ, et al. Comparison of ondansetron with ondansetron plus dexamethasone in the prevention of postoperative nausea and vomiting. *Anesth Analg*. 1994;79:961–964.
26. Baxendale BR, Vater M, Lavery KM. Dexamethasone reduces pain and swelling following extraction of third molar teeth. *Anaesthesia*. 1993; 48:961–694.
27. Barnes PJ. Anti-inflammatory actions of glucocorticoids: molecular mechanisms. *Clin Sci (Lond.)*. 1998;94:557–572.
28. Wang JJ, Ho ST, Tzeng JI, et al. The effect of timing of dexamethasone administration on its efficacy as a prophylactic antiemetic for postoperative nausea and vomiting. *Anesth Analg*. 2000;91:136–139.